10/826,679
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FILE 'WPIDS' ENTERED AT 10:29:52 ON 13 SEP 2006

=> **s fibrate**
L1 1472 FIBRATE

=> **s aldose reductase**
L2 7004 ALDOSE REDUCTASE

=> **s l1 and l2**
L3 20 L1 AND L2

=> **d l3 1-10 ibib, abs**

L3 ANSWER 1 OF 20 MEDLINE on STN
ACCESSION NUMBER: 2005578228 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 16226225
TITLE: Fibrates inhibit aldose reductase activity in the forward and reverse reactions.
AUTHOR: Balendiran Ganesaratnam K; Rajkumar Balakrishnan
CORPORATE SOURCE: Division of Immunology, Beckman Research Institute of the City of Hope National Medical Center, 1450 E. Duarte Road, Duarte, CA 91010, USA.. gbalendiran@coh.org
SOURCE: Biochemical pharmacology, (2005 Nov 25) Vol. 70, No. 11, pp. 1653-63. Electronic Publication: 2005-10-13. Journal code: 0101032. ISSN: 0006-2952.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200512
ENTRY DATE: Entered STN: 1 Nov 2005
Last Updated on STN: 22 Dec 2005
Entered Medline: 20 Dec 2005

AB Fibrates such as bezafibrate, gemfibrozil, clofibric acid, ciprofibrate and fenofibrate, are ligands for peroxisome proliferator-activated receptor alpha (PPARalpha), and are used as therapeutic agents in the treatment of hyperlipidemia. Synthesis and accumulation of sorbitol in cells due to aldose reductase (AR) activity is implicated in secondary diabetic complications. In pursuit of finding a lead compound identification to design an effective AR inhibitor employing fragment-based design-like approach, we found that this class of compounds and their nearest neighbors could inhibit AR. Bezafibrate and gemfibrozil displayed a mixed non-competitive inhibition pattern in the glyceraldehyde reduction activity and pure non-competitive inhibition pattern in the benzyl alcohol oxidation activity of AR. Clofibric acid, ciprofibrate and fenofibrate showed pure non-competitive inhibition patterns in the forward

reaction. In the reverse reaction, clofibric acid displayed a non-competitive inhibition pattern while ciprofibrate and fenofibrate displayed competitive inhibition patterns. This finding reveals for the first time a novel attribute of the fibrates in the regulation of AR activity and may be useful as lead compounds to control the function of AR in the progression and treatment of secondary diabetic complications in addition to other clinical conditions. Alternatively, these findings demonstrate that AR plays a significant role in the fibrate metabolism under various scenarios.

L3 ANSWER 2 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1162223 CAPLUS Full-text
DOCUMENT NUMBER: 143:452786
TITLE: Fibrates inhibit aldose reductase activity in the forward and reverse reactions
AUTHOR(S): Balendiran, Ganesaratnam K.; Rajkumar, Balakrishnan
CORPORATE SOURCE: Division of Immunology, Beckman Research Institute of the City of Hope National Medical Center, Duarte, CA, 91010, USA
SOURCE: Biochemical Pharmacology (2005), 70(11), 1653-1663
CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Fibrates such as bezafibrate, gemfibrozil, clofibric acid, ciprofibrate and fenofibrate, are ligands for peroxisome proliferator-activated receptor α (PPARα), and are used as therapeutic agents in the treatment of hyperlipidemia. Synthesis and accumulation of sorbitol in cells due to aldose reductase (AR) activity is implicated in secondary diabetic complications. In pursuit of finding a lead compound identification to design an effective AR inhibitor employing fragment-based design-like approach, we found that this class of compds. and their nearest neighbors could inhibit AR. Bezafibrate and gemfibrozil displayed a mixed non-competitive inhibition pattern in the glyceraldehyde reduction activity and pure non-competitive inhibition pattern in the benzyl alc. oxidation activity of AR. Clofibric acid, ciprofibrate and fenofibrate showed pure non-competitive inhibition patterns in the forward reaction. In the reverse reaction, clofibric acid displayed a non-competitive inhibition pattern while ciprofibrate and fenofibrate displayed competitive inhibition patterns. This finding reveals for the first time a novel attribute of the fibrates in the regulation of AR activity and may be useful as lead compds. to control the function of AR in the progression and treatment of secondary diabetic complications in addition to other clin. conditions. Alternatively, these findings demonstrate that AR plays a significant role in the fibrate metabolism under various scenarios.
REFERENCE COUNT: 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 3 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:15948 CAPLUS Full-text
DOCUMENT NUMBER: 142:107446
TITLE: Oxidoreductase inhibitors and methods of screening and using thereof
INVENTOR(S): Balendiran, Ganesaratnam K.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 55 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2005004225	A1	20050106	US 2004-826679		20040416
PRIORITY APPLN. INFO.:			US 2003-463629P	P	20030416

AB The present invention relates to (1) the design and synthesis of analogs to glutathione conjugates which bind to or interact with aldose reductase (AR) through unique conformations that are distinctly different from the substrates and inhibitors of AR which are members of sugar metabolism; (2) the screening of the analogs to identify those that interact with or inhibit or enhance the activity of AR; and (3) the use of AR ligands, AR inhibitors (AR antagonists) or AR enhancer (AR agonists) in the detection of AR activity, the modulation of AR activity, and the treatment of conditions in a subject in need of modulating AR activity. Such conditions include but not limited to cardiovascular disease, diabetes, atherosclerosis, cancer, neoplasm, obesity, cataract, retinopathy, keratopathy, nephropathy, neurosis, thrombosis, faulty union of corneal injury and neuropathy. Examples of the treatment include the use of fibrates as AR inhibitors to treat these conditions.

L3 ANSWER 4 OF 20 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN

ACCESSION NUMBER: 2006-558664 [57] WPIDS

DOC. NO. CPI: C2006-174253

TITLE: New fused pyrazole derivative useful as RUP25 receptor agonist or partial agonist, for treating metabolic-related disorder, e.g. dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance, obesity or hypertension.

DERWENT CLASS: B02

INVENTOR(S): BOATMAN, D P; JUNG, J; SCHRADER, T O; SEMPLE, G; SKINNER, P J

PATENT ASSIGNEE(S): (AREN-N) ARENA PHARM INC

COUNTRY COUNT: 113

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2006069242	A2	20060629	(200657)*	EN	170

RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU LV MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KM KN KP KR KZ LC LK LR LS LT LU LV LY MA MD MG MK MN MW MX MZ NA NG NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SM SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2006069242	A2	WO 2005-US46599	20051222

PRIORITY APPLN. INFO: US 2005-676521P 20050429; US 2004-638668P 20041223

AN 2006-558664 [57] WPIDS

AB WO2006069242 A UPAB: 20060906

NOVELTY - A fused pyrazole derivative (I) or its salt, hydrate, or solvate is new.

DETAILED DESCRIPTION - A fused pyrazole derivative of formula (I) or its salt, hydrate, or solvate is new. X, Z = N or CR7;

R1, R4 = T or amino-(1-6C alkylsulfonyl);

R2, R3 = T, 1-6C alkyl(thio)amido, amino-(1-6C alkylsulfonyl), arylsulfinyl, arylsulfonyl, arylthio, carbamimidoyl, 3-7C cycloalkyloxy, heterocyclyloxy, heterocyclylsulfonyl, heterocyclylcarbonyl, heteroaryl(carbonyl), 7C oxo-cycloalkyl, phenoxy, phenyl or sulfonic acid (where 1-6C alkyl is optionally substituted by 1-6C acyl(oxy), 1-6C (halo)alkoxy, 1-6C alkylamino, 1-6C (halo)alkylsulfinyl, 1-6C (halo)alkylsulfonyl, 1-6C (halo)alkylthio, amino, carbo-(1-6C alkoxy), carboxamide, carboxy, cyano, 3-7C cycloalkyl(oxy), 2-6C dialkylamino, hydroxyl, nitro, phenoxy, or phenyl); or

CR2+R3 = 3-6C cycloalkyl;

R5, R6 = T;

R7 = carbo-(1-6C alkoxy), carboxy, or tetrazol-5-yl; and

T = H, 1-6C acyl(oxy), 2-6C alkenyl, 1-6C (halo)alkoxy, 1-6C alkyl(amino), (di)1-6C alkyl(thio)carboxamide, 2-6C alkynyl, 1-6C alkylsulfonamide, 1-6C (halo)alkylsulfinyl, 1-6C (halo)alkylsulfonyl, 1-6C (halo)alkylthio, 1-6C alkyl(thio)ureyl, amino, carbo-(1-6C alkoxy), carboxamide, carboxy, cyano, 3-7C cycloalkyl, 2-6C dialkylamino, 1-6C dialkyl(thio)carboxamide, halo, 1-6C haloalkyl, heterocyclic, hydroxyl, nitro, sulfonamide, or thiol; and

provided that when X is N, then Z is CR7, and when X is CR7, then Z is N.

INDEPENDENT CLAIMS are also included for:

(1) a pharmaceutical composition comprising (I) and pharmaceutical carrier;

(2) treatment of metabolic-related disorder by administering (I) alone or in combination with DP receptor antagonist (II) to an individual;

(3) modulation of nicotinic acid receptor (RUP25 receptor) by contacting the receptor with (I);

(4) a method of raising high-density lipoprotein (HDL) in an individual, e.g. human, by administering (I) to the individual; and

(5) production of pharmaceutical composition by mixing (I) and pharmaceutical carrier.

ACTIVITY - Antilipemic; Antiarteriosclerotic; Antidiabetic; Anorectic; Hypotensive; Cerebroprotective; Vasotropic; Analgesic; Antianginal.

Test details are described but no results are given.

MECHANISM OF ACTION - RUP25 receptor agonist/partial agonist.

Test details are described but no results are given.

USE - (I) Is useful for treating metabolic-related disorder, e.g. dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance, obesity, impaired glucose tolerance, atheromatous disease, hypertension, stroke, syndrome X, heart disease, or type 2 diabetes, of human or animal body by therapy. It is also useful for raising HDL of human or animal body by therapy, and may be used for the manufacture of a medicament for treating metabolic-related disorder and a medicament for raising HDL in an individual (all claimed).

Test details are described but no results are given.

ADVANTAGE - (I) Inhibits production of free fatty acids while resulting in lower or no measurable flushing side effects. It does not cause vasodilation at doses as high as about 300 mpk as measured using known methods, and causes no measurable flushing in an individual compared to an equally effective dose of niacin. Dwg.0/0

L3 ANSWER 5 OF 20 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN

ACCESSION NUMBER: 2006-353767 [36] WPIDS

DOC. NO. CPI: C2006-115672

TITLE: Composition useful for reducing flushing induced by niacin and its analog during prevention and treatment of

lipid-associated disorder, comprising lipid altering amount of niacin or its analog, and niacin receptor partial agonist.

DERWENT CLASS: B02 B03
INVENTOR(S): BEHAN, D P; CONNOLLY, D T; RICHMAN, J
PATENT ASSIGNEE(S): (AREN-N) ARENA PHARM INC
COUNTRY COUNT: 113
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2006052569	A1	20060518	(200636)*	EN	101

RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU LV MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KM KN KP KR KZ LC LK LR LS LT LU LV LY MA MD MG MK MN MW MX MZ NA NG NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SM SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2006052569	A1	WO 2005-US39560	20051101

PRIORITY APPLN. INFO: US 2004-625536P 20041105
AN 2006-353767 [36] WPIDS
AB WO2006052569 A UPAB: 20060607

NOVELTY - A composition comprises lipid altering amount of niacin or its analog, and a niacin receptor partial agonist (I).

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) reducing flushing induced by niacin comprising administering a niacin receptor partial agonist and optionally lipid altering amount of niacin;

(2) preventing or treating a lipid-associated disorder comprising administering niacin receptor partial agonist and lipid altering amount of niacin; and

(3) a kit for preventing or treating a lipid-associated disorder comprising at least one dosage unit or pre-dosage unit of niacin receptor partial agonist and at least one dosage unit (separate dosage unit) of niacin.

ACTIVITY - Gynecological; Antipyretic; Antilipemic; Cardiant; Cerebroprotective; Vasotropic; Antiarteriosclerotic; Antianginal.

A group of mice were treated with niacin alone and an experimental group was administered with 5-(3-fluorobenzyl)-1H-pyrazole-3-carboxylic acid about 10 minutes before administration of niacin. The flushing above baseline was measured over time in both groups. The control group mice began to flush after 1.5 minutes with flush peaking at about 100 - 150% of baseline at 3 minutes and returning to about 30 - 45% within about 15 minutes. Treatment group mice resulted in 0% change from baseline at 3 minutes with change from baseline slowly increasing to 15% within 15 minutes.

MECHANISM OF ACTION - Niacin receptor partial agonist.

USE - For reducing flushing induced by niacin and its analogs during prevention and treatment of a lipid-associated disorder (claimed) e.g. atherosclerosis, heart attack (e.g. myocardial infarction), stroke, hyperlipidemia, angina, ischemic heart disease, dysmenorrhea, painful menstruation and aneurysm.

ADVANTAGE - The composition provides lipid altering amount of niacin or its analog with reduced capacity to provoke a flushing reaction. Dwg.0/0

L3 ANSWER 6 OF 20 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2006-263717 [27] WPIDS
DOC. NO. CPI: C2006-085895
TITLE: New 1-(beta)-D-glycopyranosyl)-3-substituted nitrogenous heterocyclic compound, useful for treating e.g. diabetes, glucose tolerance abnormality, diabetic complication, obesity, high insulinemia, hyperlipidemia and hypercholesterolemia.
DERWENT CLASS: B02
INVENTOR(S): KIKUCHI, N; TERANISHI, H
PATENT ASSIGNEE(S): (KISP) KISSEI PHARM CO LTD; (OHNO-I) OHNO K
COUNTRY COUNT: 112
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2006035796	A1	20060406	(200627)*	JA	128

RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU LV MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KM KP KR KZ LC LK LR LS LT LU LV LY MA MD MG MK MN MW MX MZ NA NG NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SM SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2006035796	A1	WO 2005-JP17807	20050928

PRIORITY APPLN. INFO: JP 2005-125257 20050422; JP 2004-283106 20040929
AN 2006-263717 [27] WPIDS
AB WO2006035796 A UPAB: 20060426
NOVELTY - 1-(beta)-D-Glycopyranosyl)-3-substituted nitrogenous heterocyclic compounds (I), and their prodrugs, salts, hydrates, and solvates, are new.
DETAILED DESCRIPTION - 1-(beta)-D-Glycopyranosyl)-3-substituted nitrogenous heterocyclic compounds of formula (I), and their prodrugs, salts, hydrates, and solvates, are new.
Ring A = aryl or heteroaryl having optional substituent;
Q1-Q5 = H or substituent bonded to carbon or nitrogen atom;
E = single bond, alkylene group, -O-, -S-, or -NH-;and
R = methyl, ethyl, fluoromethyl or hydroxymethyl group.
Excluded are 1-(beta)-D-glucopyranosyl)-3-(2-thiazolyl) indole and 1-(beta)-D-glucopyranosyl)-6-methoxy-3-(2-thiazoyl) indole.
An INDEPENDENT CLAIM is also included for a pharmaceutical composition comprising (I) optionally in combination with other active agents.
ACTIVITY - Antidiabetic; Anorectic; Antilipemic; Antiarteriosclerotic; Hypotensive; Cardiant; Antiinflammatory; Antigout.
MECHANISM OF ACTION - Inhibitor of sodium glucose cotransporter (SGLT) activation; Inhibitor of glucose absorption; Inhibitor of galactose absorption; Inhibitor of glucose re-absorption (all claimed)
Diabetic condition was induced in SD rat (8 weeks old) by injecting streptozotocin (45 mg/kg). To the control group, only distilled water was orally administered. The test group was orally administered with the liquid

feed (323 ml) containing blend of dextrin and maltose. A blood sampling was performed. Blood sugar was determined. Results showed that blood glucose was reduced from 374 plus or minus 20 mg/dl (at 0.5 hours) to 347 plus or minus 23 mg/dl (at 1 hour) in test group.

USE - As glucose or galactose absorption inhibitor, as glucose re-absorption inhibitor, and for preventing or treating post-prandial hyperglycemia, diabetes, glucose tolerance abnormality, diabetic complication, obesity, high insulinemia, hyperlipidemia, hypercholesterolemia, galactosemia, hypertriglyceridemia, lipid metabolism disorder, atherosclerosis disease, hypertension, congestive cardiac failure, edema, hyperuricemia, and gout, and for suppressing the occurrence of diabetes from glucose tolerance abnormality (all claimed).

ADVANTAGE - (I) effectively inhibits SGLT activation. Dwg.0/0

L3 ANSWER 7 OF 20 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2006-047142 [05] WPIDS
DOC. NO. CPI: C2006-017607
TITLE: New nitrogenous fused ring derivatives, their salts or prodrugs useful for preventing and treating diseases resulting from hyperglycemia such as diabetes or its complication, obesity, hyper insulinemia and hyperlipidemia.
DERWENT CLASS: B02
INVENTOR(S): FUSHIMI, N; ISAJI, M; ITO, F; SHIMIZU, K; TERANISHI, H; YONEKUBO, S
PATENT ASSIGNEE(S): (KISP) KISSEI PHARM CO LTD
COUNTRY COUNT: 109
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2005085267	A1	20050915	(200605)*	JA	169

RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SM SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2005085267	A1	WO 2005-JP4145	20050303

PRIORITY APPLN. INFO: JP 2004-61426 20040304
AN 2006-047142 [05] WPIDS
AB WO2005085267 A UPAB: 20060120
NOVELTY - Nitrogenous fused ring derivatives (I), their salts or prodrugs are new.

DETAILED DESCRIPTION - Nitrogenous fused ring derivatives of formula (I), their salts or prodrugs are new.

R1 = hydrogen, 1-6C alkyl, halo (1-6C alkyl), hydroxy (1-6C alkyl), dihydroxy (1-6C alkyl), 1-6C alkoxy (1-6C alkyl), 2-7C alkoxycarbonyl (1-6C alkyl), carboxy (1-6C alkyl), 2-6C alkenyl, or optionally substituted 3-7C

cycloalkyl, 3-7C cycloalkyl (1-6C alkyl), 6-10C aryl or 6-10C aryl (1-6C alkyl) groups;

R2 = H, halogen or 1-6C alkyl;

R3 and R4 = H, hydroxyl, halogen, 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 1-6C alkoxy, 1-6C alkenyl oxy, 1-6C alkylthio, 2-6C alkenyl thio, halo (1-6C alkyl), halo (1-6C alkoxy), halo (1-6C alkylthio), hydroxy (1-6C alkyl), hydroxy (2-6C alkenyl), hydroxy (1-6C alkoxy), hydroxy (1-6C alkylthio), carboxy, carboxy (1-6C alkyl), carboxy (2-6C alkenyl), carboxy (1-6C alkoxy), carboxy (1-6C alkylthio), 2-7C alkoxycarbonyl, 2-7C alkoxycarbonyl (1-6C alkyl), 2-7C alkoxycarbonyl (2-6C alkenyl), 2-7C alkoxycarbonyl (1-6C alkoxy), 2-7C alkoxycarbonyl (1-6C alkylthio), 1-6C alkyl sulfinyl, 1-6C alkyl sulfonyl;

Ring A = 6-10C aryl or heteroaryl group of formula (G-1) or (G-2);

E1 = H, fluorine or hydroxyl;and

E2 = H, fluorine, methyl or hydroxymethyl.

Full definitions are given in the definition section.

INDEPENDENT CLAIMS are also included for the following:

(1) pharmaceutical composition containing the nitrogenous fused ring derivative (I), its salt or prodrug as active ingredient;

(2) human sodium glucose transporter (SGLT) activation inhibitor comprising the nitrogenous fused ring derivative (I), its salt or prodrug as active ingredient;

(3) suppression of postprandial hyperglycemia, which involves administering the nitrogenous fused ring derivative (I), its salt or prodrug;

(4) prevention or treatment of diseases resulting from hyperglycemia, which involves administering nitrogenous fused ring derivative (I), its salt or prodrug;

(5) method for preventing diabetes in patients having impaired glucose tolerance, which involves administering nitrogenous fused ring derivative (I), its salt or prodrug to the patient;

(6) use of nitrogenous fused ring derivative (I), its salt or prodrug for producing the pharmaceutical composition; and

(7) preparation of the pharmaceutical composition, which involves mixing the nitrogenous fused ring derivative (I), its salt or prodrug with medical agents selected from insulin sensitizer, sugar absorption inhibitor, biguanide, insulin secretagogue, SGLT2 active inhibitor, insulin or its analog, glucagon receptor antagonist, insulin receptor kinase stimulant, tripeptidyl peptidase II inhibitor, dipeptidyl peptidase IV inhibitor, protein tyrosine phosphatase-1B inhibitor, glycogen phosphorylase inhibitor, glucose-6-phosphatase inhibitor, fructose-bis phosphatase inhibitor, pyruvate-dehydrogenase inhibitor, hepatic glucose synthesis inhibitor, D-chiroinositol, glycogen-synthase kinase-3 inhibitor, glucagon type peptide-1 or its analog, glucagon type peptide-1 agonist, amylin, its analog or its agonist, aldose reductase inhibitor, protein-kinase C inhibitor, (gamma)-aminobutyric-acid receptor antagonist, sodium channel antagonist, transcription-factor NF-kappa B inhibitor, lipid peroxidase inhibitor, N-acetylated-(alpha)-linked acid dipeptidase inhibitor, insulin like growth factor, platelet-derived growth factor or its analog, insulin-like-growth-factor-1, epidermal growth factor, nerve growth factor, carnitine derivative, uridine, 5-hydroxy-1-methyl hydantoin, EGB-761, Y-128, antidiarrhoeal, laxative, hydroxymethyl glutaryl coenzyme A reductase inhibitor, fibrate-type compound, (beta)3-adrenoreceptor agonist, acyl coenzyme A, cholesterol transacylase inhibitor, probucol, thyroid-hormone receptor agonist, cholesterol absorption inhibitor, lipase inhibitor, microsome triglyceride transfer protein inhibitor, lipoxygenase inhibitor, carnitine palmitoyl transferase inhibitor, low specific gravity lipoprotein receptor agonist, nicotinic acid derivative, bile acid adsorbent, sodium conjugation bile acid transporter inhibitor, cholesterol ester transmission protein inhibitor, anorectic, angiotensin-converting-enzyme inhibitor, neutral endopeptidase inhibitor, angiotensin II receptor antagonist, endothelin converting-enzyme inhibitor, endothelin

receptor antagonist, diuretic, calcium antagonist, vasodilation property antihypertensive agent, neuroleptic, central antihypertensive agent, (alpha)2-adrenoreceptor agonist, antiplatelet agent, uric acid antagonist, uric acid eliminant and/or urine alkalizer.

ACTIVITY - Antidiabetic; Anorectic; Antilipemic; Antiarteriosclerotic; Hypotensive; Cardiant; Antiinflammatory; Antigout.

MECHANISM OF ACTION - Sodium-Glucose-Transporter-Inhibitor-1; Sodium-Glucose-Transporter-Inhibitor-2 (both claimed); Insulin-Antagonist; Cholesterol-Antagonist; Triglyceride-Antagonist. The SGLT-2 inhibitory effect of 3-(beta)-D-glucopyranosyloxy)-1-(2-hydroxyethyl)-4-(2-phenyl ethyl)-1H-pyrazolo (3,4-b) pyridine (Ia) was evaluated using cloned human SGLT-2 by measuring the methyl-(alpha)-D-glucopyranoside uptake inhibition activity. The compound (Ia) was found to have IC50 value of 68 nM.

USE - For preventing and treating postprandial hyperglycemia and diseases resulting from hyperglycemia such as diabetes, impaired glucose tolerance, diabetic complication, obesity, hyper insulinemia, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, lipid metabolism disorder, atherosclerosis, hypertension, congestive cardiac failure, edema, hyperuricemia and gout (all claimed).

ADVANTAGE - The novel nitrogenous fused ring derivative has excellent human SGLT action inhibitory effect, and effectively suppresses reabsorption of glucose in kidney and absorption of carbohydrate in the small intestine.

Dwg.0/0

L3 ANSWER 8 OF 20 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN

ACCESSION NUMBER: 2005-425184 [43] WPIDS
DOC. NO. CPI: C2005-130498
TITLE: New 4-oxo-4,5-dihydro-furan-2-carboxylic acid derivatives useful for the treatment of e.g. hypertension, coronary heart disease, atherosclerosis, diabetes, insulin resistance, obesity, impaired glucose tolerance and stroke.
DERWENT CLASS: B03
INVENTOR(S): JOHNSON, B R; JUNG, J; SEMPLE, G
PATENT ASSIGNEE(S): (AREN-N) ARENA PHARM INC
COUNTRY COUNT: 108
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2005051937	A2	20050609	(200543)*	EN	76

RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2005051937	A2	WO 2004-US38920	20041118

PRIORITY APPLN. INFO: US 2003-524269P 20031121
AN 2005-425184 [43] WPIDS

AB WO2005051937 A UPAB: 20050707
NOVELTY - 4-Oxo-4,5-dihydro-furan-2-carboxylic acid derivatives (I) are new.
DETAILED DESCRIPTION - 4-Oxo-4,5-dihydro-furan-2-carboxylic acid derivatives of formula (I) and their salts, hydrates and solvates, are new.
R1 = H or 1-6C alkyl;
R2 = H, halo or 1-4C-(halo)alkyl;
R3 = (hetero)aryl, 3-7C (hetero)cycloalkyl or 3-7C (hetero)cycloalkenyl (all optionally mono- to penta-substituted by T or optionally substituted (hetero)aryl);
T = 1-6C acyloxy, 2-6C alkenyl, 1-6C-(halo)alkoxy, 1-6C-(halo)alkyl, 1-6C alkylcarboxamide, 2-6C alkynyl, 1-6C alkysulfonamide, 1-6C-(halo)alkylsulfinyl, 1-6C-(halo)alkylsulfonyl, 1-6C-(halo)alkylthio, 1-6C alkylureyl (sic), 1-6C alkylamino, amino, carbo-1-6C alkoxy, carboxamide, cyano, 3-7C cycloalkyl, 2-6C dialkylamino, 2-6C dialkylcarboxamide, 2-6C dialkylsulfonamide, halo, OH, nitro or thiol; and
R4 = H, ethyl, n-propyl, 4-6C-alkyl 1-6C-haloalkyl or 3-6C cycloalkyl (all optionally mono- to penta-substituted by T); or
R3 = a substituted phenyl, 2-chlorophenyl, 3-chlorophenyl, naphthyl, 3-7C-(hetero)cycloalkenyl or 3-7C (hetero)cycloalkyl (all optionally mono- to penta-substituted by T or optionally substituted (hetero)aryl); and
R4 = H, 1-6C-(halo)alkyl or 3-6C cycloalkyl (all optionally mono- to penta-substituted by T)
ACTIVITY - Antilipemic; Antiarteriosclerotic; Cardiant; Antidiabetic; Anorectic; Hypotensive; Cerebroprotective; Vasotropic; Analgesic; Antianginal; Metabolic.
MECHANISM OF ACTION - RUP25 (nicotinic acid receptor) modulator; RUP25 receptor agonist; RUP25 receptor partial agonist; Lipolysis inhibitor.
The biological activity of (I) as RUP25 receptor agonist was determined by cAMP whole cell method using CHO cell stably transfected with hRU025 receptor, and showed EC50 of 30 nM - 20 mu M.
USE - In the manufacture of a medicament for the treatment of a metabolic-related disorder such as dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance, obesity, impaired glucose tolerance, atheromatous disease, hypertension, stroke, syndrome X, heart disease and type 2 diabetes, in a mammal (including humans and animals) (claimed). Also useful in the preparation of radio-labeled compounds useful for radio-imaging and in vivo and in vitro assays for localizing and quantitating RUP25 in tissue samples and identifying Rup25 ligands.
ADVANTAGE - The compounds are potent modulators (preferably agonists or partial agonists) of nicotinic acid RUP25 receptor, and result in raising the HDL by lowering free fatty acid release; while producing fewer side effects than those associated with the nicotinic acid (niacin) such as flushing, free fatty acid rebound and liver toxicity. The compounds inhibit lipolysis that is mediated by activation of hormone sensitive lipase within adipocytes by increase in cAMP. The compounds are present in the form of R or S enantiomers. The radio-labeled compounds have EC50 for binding to RUP25 receptor of (less than 500, preferably less than 100, especially less than 10, particularly less than 0.1) mu M. Dwg.0/0

L3 ANSWER 9 OF 20 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2005-152341 [16] WPIDS
DOC. NO. CPI: C2005-049341
TITLE: 5-Substituted 2H-pyrazole-3-carboxylic acid derivative used as agonists for the nicotinic acid receptor RUP25 for the treatment of metabolic-related disorder, e.g. dyslipidemia, obesity, hypertension, stroke, Syndrome X and type 2 diabetes.
DERWENT CLASS: B03
INVENTOR(S): AVERBUJ, C; DECAIRE, M; GHARBAOUI, T; SEMPLE, G; SHIN, Y;

SKINNER, P; SKINNER, P J
PATENT ASSIGNEE(S): (AREN-N) ARENA PHARM INC
COUNTRY COUNT: 109
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2005011677	A1	20050210	(200516)*	EN	130
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW					
EP 1633351	A1	20060315	(200620)	EN	
R: AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LU MC NL PL PT RO SE SI SK TR					
AU 2004260636	A1	20050210	(200654)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2005011677	A1	WO 2004-US18389	20040610
EP 1633351	A1	EP 2004-776418	20040610
		WO 2004-US18389	20040610
AU 2004260636	A1	AU 2004-260636	20040610

FILING DETAILS:

PATENT NO	KIND	PATENT NO
EP 1633351	A1 Based on	WO 2005011677
AU 2004260636	A1 Based on	WO 2005011677

PRIORITY APPLN. INFO: US 2003-478664P 20030613
AN 2005-152341 [16] WPIDS
AB WO2005011677 A UPAB: 20050308
NOVELTY - 5-Substituted 2H-pyrazole-3-carboxylic acid derivative (I), or its salt, solvate or hydrate, is new.

DETAILED DESCRIPTION - 5-Substituted 2H-pyrazole-3-carboxylic acid derivative of formula (I), or its salt, solvate or hydrate, is new (i)

W, Y = straight or branched 1-5C alkylene optionally containing one double bond, one triple bond or carbonyl, wherein the alkylene group is optionally substituted with halo, hydroxyl, 1-4C alkyl, 1-4C haloalkyl or 1-4C alkoxy;

X = -NR3C(O)-, -C(O)NR3, -NR3S(O)2-, -S(O)2NR3-, -NR3C(O)NR4-, -NR3C(O)O-, -OC(O)NR3-, -NR3-, -C(O)-, -CH(OH)-, -C(NH)-, -O-, -S-, -S(O)- or -S(O)2-;

R3, R4 = H, 1-4C alkyl, phenyl or heteroaryl, where each of the alkyl, phenyl and heteroaryl are optionally substituted with 1-5 substituents selected from halo, hydroxyl, thiol, cyano, nitro, 1-4C haloalkyl, amino, 1-4C alkylamino, di-1-4C-alkylamino, 1-4C alkyl, 1-4C alkoxy, 2-4C alkenyl, 2-4C alkynyl, 1-4C haloalkoxy, 1-4C alkylthio, 1-4C alkylsulfinyl, 1-4C alkylsulfonyl, 1-4C haloalkylthio, 1-4C haloalkylsulfinyl, or 1-4C haloalkylsulfonyl;

Z = H, halo, phenyl or heteroaryl, where the phenyl and heteroaryl are optionally substituted with 1-5 substituents same as that of R3 and R4;

R1 = H, hydroxyl, halogen, 1-4C alkyl or 1-4C haloalkyl;

R2 = H or 1-8C alkyl;

n, m = 0-1;
(ii)
R1 and R2 = H, then -(W)n-X-(Y)m-Z together is not CO2H, C(O)-C6H4-p-O-C8H17, OCH2CH3, OH, CH2CH2CH2CH2CO2H, CH2CH2CH2CO2H, CH2CO2H and CH2CH2CO2H;
(iii)
R1 = CH3;
R2 = H, then -(W)n-X-(Y)m-Z together is not CH2CO2H, C(O)CH=CH C6H5, C(O)C6H4-p-OCH3, CO2H, C(O)CH3, C(O)C6H4-o-CH3, C(O)C6H4-o-Br, C(O)C6H4-o-Cl, and C(O)C6H5;
(iv)
R1 = Br;
R2 = H, then -(W)=-X-(Y)m-Z together is not CO2H; (v)
R1 = OH;
R2 = H, then -(W)n-X-(Y)m-Z together is not CO2H; (vi)
R1 = H;
R2 = CH3, then -(W)n-X-(Y)m-Z together is not 2,6-dichloro-4-trifluoromethylphenoxy, C(O)NH-C6H4-p-OCH2CH3, NHC(O)CH(CH3)2, SCH3, C(O)-C6H4-p-O-C8H17, SCH2CH3, C(O)N'rrlC6Hs, CH(OCH3)2, CH2OC(O)CH3, CO2H, CO2CH3, C(O)C6H4-p-NO2, C(O)C6H5, CH2CH2CO2CH3, CH2CH2CH2CH2CO2CH3, CH2CH2CH2CO2CH3 and CH2CO2CH3;
(vii)
R1 = OH;
R2 = CH3, then-(W)n-X-(Y)m-Z together is not CH2OCH2C6H5, CH2OCH(CH3)2 and CH2OH;
(viii)
R2 = CH3, then R1 is not CH3 and -(W)n-X-(Y)m-Z together is not 2,6-dichloro-4-trifluoromethylphenoxy; R1 is not I and -(W)n-X-(Y)m-Z together is not CO2C(CH3)3; R1 is not C(CH3)3 and -(W)n-X-(Y)m-Z together is not formyl; R1 is not Br and -(W)n-X-(Y)m-Z together is not CO2CH3; and R1 is not CH2CH2CH2CH3 and -(W)n-X-(Y)m-Z together is not formyl; (ix)
R1 = H;
R2 = CH2CH3 then -(W)n-X-(Y)m-Z together is not CH2SCH2CH3, OCH2CH2CH=CH2, CH2CH2CH2OH, CH2CH2CHO, CO2CH2CH3, OCH3, C(O)CH2Br, CO2C8H17, formyl, OH, CH2N(CH2CH2Cl)2, CH(CH3)OC(O)CH3, CH2OH, CH2OC(O)CH3, C(O)CH3, C(O)C6H5, and C(O)NHCH2CO2CH2CH3; (x)
R1 = CH3;
R2 = CH2CH3, then -(W)n-X-(Y)m-Z together is not CH(OH)C6H4-p- N(CH3)2, C(O)CH2C(O)CH3, CO2CH2C6H5, CO2CH3, C(O)CH2CH2CH3, C(O)CH3, C(O)C6H4-p-OCH3, C(O)C6H4-o-Br, C(O)C6H4-p-Cl, C(O)C6H4-o-Cl, C(O)CH2C6H5 and C(O)C6H5;
(xi)
R2 = CH2CH3, then R1 is not I and -(W)n-X-(Y)m-Z together is not CO2CH2CH3; R1 is not CF3 and -(W)n-X-(Y)m-Z together is not CO2CH2CH3; and R1 is not Br and -(W)n-X-(Y)m-Z together is not CO2CH2CH3; (xii)
R1 = OH;
R2 = CH2CH3, then -(W)n-X-(Y)m-Z together is not C(O)C6H5, C(O)NH2 and CO2CH2CH3;
(xiii)
R1 = H;
R2 = C(CH3)3 then -(W)n-X-(Y)m-Z together is not CO2C(CH3)3, C(O)NHC(O)CH3 and C(O)NH2;
(xiv)
R1 = OH;
R2 = CH2CH2CH2CH3, then -(W)n-X-(Y)m-Z together is not C(O)C6H5;and (xv)
X = -NR3-;
n = 1.

INDEPENDENT CLAIMS are also included for:

(1) a pharmaceutical composition comprising carrier in combination with compound (I);

(2) a method for prophylaxis or treatment of metabolic-related disorder in individual in need of prophylaxis or treatment, comprising administering compound (I) or the above pharmaceutical composition;

(3) a method of modulating RUP25 receptor in individual comprising contacting the receptor with compound (I); and

(4) a method of producing a pharmaceutical composition comprising mixing compound (I) and carrier or excipient.

ACTIVITY - Antilipemic; Antiarteriosclerotic; Antidiabetic; Anorectic; Hypotensive; Cerebroprotective; Vasotropic; Analgesic; Antianginal; Cardiant.

MECHANISM OF ACTION - Nicotinic acid receptor agonist; Alpha-glycosidase inhibitor; Aldose reductase inhibitor; HMG-CoA reductase inhibitor; Squalene synthesis inhibitor; Angiotensin converting enzyme inhibitor. Lipolysis assays were done following isolation of adipocytes from human. An elevation of intracellular cAMP levels and concomitant activation of lipolysis via hormone sensitive lipase was accomplished using isoproterenol, forskolin, and/or 3-isobutyl-1-methyl-xanthine (IBMX). Lipolysis was allowed to continue for the desired time in the presence of nicotinic acid. Results showed that the nicotinic acid inhibited intracellular lipolysis.

USE - The novel compound is used for producing a medicament or pharmaceutical composition for use in prophylaxis or treatment metabolic-related disorder, such as dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance, obesity, impaired glucose tolerance, atheromatous disease, hypertension, stroke, Syndrome X, heart disease and type 2 diabetes. It is also used for modulating RUP25 receptor (all claimed).

ADVANTAGE - The novel compound has improved therapeutic activity with minimal side effects.

Dwg.0/10

L3 ANSWER 10 OF 20 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN

ACCESSION NUMBER: 2005-081428 [09] WPIDS

DOC. NO. CPI: C2005-028182

TITLE: New pyrazole derivatives, used to treat e.g. diabetes, hyperlipidemia, atherosclerosis, hypertension, gout and nephritis, are sodium glucose co transporter inhibitors.

DERWENT CLASS: B03

INVENTOR(S): FUJIKURA, H C R L; ISAJI, M; KIKUCHI, N; TAZAWA, S; YAMATO, T; FUJIKURA, H

PATENT ASSIGNEE(S): (KISP) KISSEI PHARM CO LTD

COUNTRY COUNT: 109

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2004113359	A1	20041229	(200509)*	JA	105
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW					
EP 1637539	A1	20060322	(200621)	EN	
R: AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LU MC NL PL PT RO SE SI SK TR					
JP 2005507253	X	20060727	(200650)		63

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE

WO 2004113359	A1	WO 2004-JP8695	20040615
EP 1637539	A1	EP 2004-746165	20040615
		WO 2004-JP8695	20040615
JP 2005507253	X	WO 2004-JP8695	20040615
		JP 2005-507253	20040615

FILING DETAILS:

PATENT NO	KIND		PATENT NO
EP 1637539	A1	Based on	WO 2004113359
JP 2005507253	X	Based on	WO 2004113359

PRIORITY APPLN. INFO: JP 2003-175663 20030620

AN 2005-081428 [09] WPIDS

AB WO2004113359 A UPAB: 20050207

NOVELTY - Pyrazole derivatives (I) are new.

DETAILED DESCRIPTION - Pyrazole derivatives of formula (I) and their salts and prodrugs are new.

R1 = 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 1-8C cycloalkyl or 2-9C heterocycloalkyl (all optionally substituted by (A)), or 6-10C aryl group or 1-9C heteroaryl (both optionally substituted by (B));

Q, T' = group of formula (Ia)-(Ie), -Z'-Ar', alicyclic amino (optionally substituted by (A)) or aromatic amino group (optionally substituted by (B));

R = 3-8C cycloalkyl or 2-9C heterocycloalkyl (both optioanally substituted by (A)) or 6-10C aryl or 1-9C heteroaryl (both optionally substituted by (B));

A = halogen, nitro, cyano, oxo, -G1, -OG2, -SG2, -N(G2)2, -C(=O)G2, -C(=O)OG2, -C(=O)N(G2)2, -S(=O)2G2, -S(=O)2OG2, -S(=O)2N(G2)2, -S(=C)G1, -OC(=O)G1, -OC(=O)N(G2)2, -NHC(=0)G2, -OS(=O)2G1 -NHS(=O)G1 or -C(=O) NHS(=O)2G1;

B = halogen, nitro, cyano, -G1, -OG2, -SG2, -N(G2)2, -G3OG4, -G3N(G4)2, -C(=O)G2, -C(=O)OG2, -C(=O)N(G2)2, -S(=0)2G2, -S(=O)2OG2, -S(=O)2N(G2)2, -C(=O)G1, -OC(=O)G1, -OC(=O)N(G2)2, -NHC(=O)G2, -OS(=O)2G1, -NHS(=O)2G1 or -C(=O) NHS(=O)2G1;

G1 = 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-8C cycloalkyl, 6-10C aryl group, 2-9C heterocycloalkyl (optionally substituted by (C)) or 1-9C heteroaryl group(optionally substituted by (D));

G2 = 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-8C cycloalkyl, 2-9C heterocycloalkyl group (optionally substituted by (C)) or 6-10C aryl group or 1-9C heteroaryl (optionally substituted by (D)); G3 = 1-6C alkyl;

G4 = 1-6C alkyl group (optionally substituted by (C));

(C) = halogen, a nitro, cyano, oxo, -G5, -OG6, -SG6, -N(G6)2, -C(=O)G6, -C(=O)OG6, -C(=O)N(G6)2, -S(=O)2G6, -S(=O)2OG6, -S(=O)2N(G6)2, -S(=O)G5, -OC(=O)G5, -OC(=O)N(G6)2, -NHC(=O)G6, -O(=O)2G5, -NHS(=O)2G5, and -C(=O) NHS(=O)2G5;

(D) = halogen, nitro, cyano, -G5, -OG6, -SG6, -N(G6)2, -C(=O) G6, -C(=O) OG6, -C(=O) N(G6)2, -S(=O)2G6, -S(=)2O G6, -C(=O)2N (G6)2, and -S(=O) G5, -OC(=O) G5, -OC(=O) N(G6)2, -NHC(=O) G6, -OS(=O)2G5, -NHS(=O)2G5, or -C(=O) NHS(=O)2G5;

G5 = 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-8C cycloalkyl, 6-10C aryl, 2-9C heteroycloalkyl, or 1-9C heteroaryl;

G6 = H, 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-8C cycloalkyl, 6-10C aryl, 2-9C heterocycloalkyl or 1-9C heteroaryl;

Ar' = 6-10C aryl or 1-9C heteroaryl (both optionally substituted by (B));

Z' = -O-, -S- or -NY'; and

Y' = H or 1-6C alkyl.

An INDEPENDENT CLAIM is also included for pharmaceutical compositions (II), comprising (I) as an active ingredient.

ACTIVITY - Antidiabetic; Anorectic; Antilipemic; Antiar- teriosclerotic; Hypotensive; Cardiovascular-Gen.; Antiinflammatory; Vasotropic; Analgesic; Antianginal; Antigout; Nephrotropic.

No biological data is given.

MECHANISM OF ACTION - Inhibitor of human sodium/glucose cotransporter (SGLT).

USE - For pharmaceutical composition for treating diabetes, after meal hyperglycemia, glucose-tolerance-abnormality, diabetic-complication, obesity, high insulinemia, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, lipid metabolism disorder, atherosclerosis disease, hypertension, congestive cardiac failure, and edema property disease and metabolic acidosis, syndrome X, hyperuricemia, gout and nephritis (all claimed).

ADVANTAGE - (I) suppresses reabsorption or cell uptake of glucose, fructose and/or mannose in kidney, and other saccharides in small intestine.

Dwg.0/2

=> **d his**

(FILE 'HOME' ENTERED AT 10:29:31 ON 13 SEP 2006)

FILE 'MEDLINE, CAPLUS, WPIDS' ENTERED AT 10:29:52 ON 13 SEP 2006
L1 1472 S FIBRATE
L2 7004 S ALDOSE REDUCTASE
L3 20 S L1 AND L2

=> **s l1/thu**
'THU' IS NOT A VALID FIELD CODE
'THU' IS NOT A VALID FIELD CODE
L4 0 L1/THU

=> **s cancer**
L5 910967 CANCER

=> **s l1 and l5**
L6 63 L1 AND L5

=> **s l6 not py>2004**
L7 23 L6 NOT PY>2004

=> **d l7 1-10 ibib, abs**

L7 ANSWER 1 OF 23 MEDLINE on STN
ACCESSION NUMBER: 2004273229 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 15172993
TITLE: Diminished hepatocellular proliferation in mice humanized for the nuclear receptor peroxisome proliferator-activated receptor alpha.
AUTHOR: Cheung Connie; Akiyama Taro E; Ward Jerrold M; Nicol Christopher J; Feigenbaum Lionel; Vinson Charles; Gonzalez Frank J
CORPORATE SOURCE: Laboratory of Metabolism, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, USA.
CONTRACT NUMBER: N01-C0-56000
SOURCE: Cancer research, (2004 Jun 1) Vol. 64, No. 11, pp. 3849-54. Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200407
ENTRY DATE: Entered STN: 3 Jun 2004
Last Updated on STN: 28 Jul 2004
Entered Medline: 26 Jul 2004

AB Lipid-lowering fibrate drugs function as agonists for the nuclear receptor peroxisome proliferator-activated receptor alpha (PPARalpha). Sustained activation of PPARalpha leads to the development of liver tumors in rats and mice. However, humans appear to be resistant to the induction of peroxisome proliferation and the development of liver cancer by fibrate drugs. The molecular basis of this species difference is not known. To examine the mechanism determining species differences in peroxisome proliferator response between mice and humans, a PPARalpha-humanized mouse line was generated in which the human PPARalpha was expressed in liver under control of the tetracycline responsive regulatory system. The PPARalpha-humanized and wild-type mice responded to treatment with the potent PPARalpha ligand Wy-14643 as revealed by induction of genes encoding peroxisomal and mitochondrial fatty acid metabolizing enzymes and resultant decrease of serum triglycerides. However, surprisingly, only the wild-type mice and not the PPARalpha-humanized mice exhibited hepatocellular proliferation as revealed by elevation of cell cycle control genes, increased incorporation of 5-bromo-2'-deoxyuridine into hepatocyte nuclei, and hepatomegaly. These studies establish that following ligand activation, the PPARalpha-mediated pathways controlling lipid metabolism are independent from those controlling the cell proliferation pathways. These findings also suggest that structural differences between human and mouse PPARalpha are responsible for the differential susceptibility to the development of hepatocarcinomas observed after treatment with fibrates. The PPARalpha-humanized mice should serve as models for use in drug development and human risk assessment and to determine the mechanism of hepatocarcinogenesis of peroxisome proliferators.

L7 ANSWER 2 OF 23 MEDLINE on STN
ACCESSION NUMBER: 2003610251 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 14694285
TITLE: Statins and stroke prevention.
AUTHOR: Amarenco Pierre; Lavallee Philippa; Touboul Pierre-Jean
CORPORATE SOURCE: Department of Neurology and Stroke Center, Bichat-Claude-Bernard University Hospital and Medical School, Denis-Diderot University-Paris VII, Paris, France.. amarenco@ccr.jussieu.fr
SOURCE: Cerebrovascular diseases (Basel, Switzerland), (2004) Vol. 17 Suppl 1, pp. 81-8. Ref: 43
Journal code: 9100851. ISSN: 1015-9770.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200402
ENTRY DATE: Entered STN: 25 Dec 2003
Last Updated on STN: 2 Mar 2004
Entered Medline: 26 Feb 2004

AB Four randomized trials with a statin and one trial with a fibrate showed a modest but significant absolute reduction in the incidence of stroke in patients with a previous myocardial infarction. The reasons for the positive effect of statins on stroke end-point are unclear since, paradoxically, the link between serum cholesterol level and stroke has never been fully

established. Furthermore, the positive results of statins trials were mainly obtained in patients with an average or a low serum cholesterol level. This suggests nonhypolipidemic effects of these drugs, so-called pleiotropic effects, acting on the biologic promoters of plaque instability. Statins have a good overall safety profile with no increase of hemorrhagic stroke and no increase in cancer. They have positive effects in primary prevention of cardiovascular disease in high-risk young as well as elderly populations. Statins reduced stroke incidence in high-risk (mainly CHD, diabetics and hypertensives) population even with a normal baseline blood cholesterol level, which argues for a global cardiovascular risk-based treatment strategy. In patients with prior strokes, statins likely reduce the incidence of cononary events, but it is not yet proven that statins actually reduce the incidence of recurrent strokes in secondary prevention. If current hypotheses are verified by ongoing trials, we may expect between 20 to 30 more stroke events avoided per 1,000 patients treated during 2 years with a lipid-lowering agent, which adds to the 28 stroke events prevented with an antiplatelet agent over the same time period. This would be one of the most significant advances in stroke and vascular dementia prevention since the era of aspirin therapy.

L7 ANSWER 3 OF 23 MEDLINE on STN
ACCESSION NUMBER: 2002407202 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 12161004
TITLE: The peroxisome proliferator-activated receptor alpha (PPARalpha): role in hepatocarcinogenesis.
AUTHOR: Gonzalez Frank J
CORPORATE SOURCE: National Cancer Institute, National Institutes of Health, Building 37, Room 3E-24, Bethesda, MD 20892, USA.. fjgonz@helix.nih.gov
SOURCE: Molecular and cellular endocrinology, (2002 Jul 31) Vol. 193, No. 1-2, pp. 71-9. Ref: 73
Journal code: 7500844. ISSN: 0303-7207.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200306
ENTRY DATE: Entered STN: 6 Aug 2002
Last Updated on STN: 14 Jun 2003
Entered Medline: 13 Jun 2003

AB The peroxisome proliferator-activated receptor alpha (PPARalpha) is a member of the nuclear receptor superfamily and mediates most of the known biological effects of peroxisome proliferators. The latter represents a large group of chemicals that include the fibrate hyperlipidemic drugs, the pthalate plasticizers, various solvents and degreasing agents, and endogenous hormones and fatty acids. Peroxisome proliferators are classical members of the nongenotoxic group of chemical carcinogens that do not require metabolic activation to electrophiles in order to exert their harmful effects. These chemicals are of particular concern to regulatory agencies since they can only be detected by long-term carcinogen bioassays using rodents. The mechanism of the carcinogenic action of peroxisome proliferators is beginning to emerge. PPARalpha-null mice are resistant to hepatocarcinogenesis indicating that this receptor is necessary for cancer. However, recent studies indicate that Kupffer cells, in a PPARalpha independent manor, are required for the major effects of peroxisome proliferators on cell proliferation. An interaction between PPARalpha and estrogen carcinogenesis has also been elucidated.

L7 ANSWER 4 OF 23 MEDLINE on STN
ACCESSION NUMBER: 2001553120 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 11599634
TITLE: How well tolerated are lipid-lowering drugs?.
AUTHOR: Tomlinson B; Chan P; Lan W
CORPORATE SOURCE: Department of Medicine and Therapeutics, Chinese University of Hong Kong, Prince of Wales Hospital, Shatin.. btomlinson@cuhk.edu.hk
SOURCE: Drugs & aging, (2001) Vol. 18, No. 9, pp. 665-83. Ref: 185
Journal code: 9102074. ISSN: 1170-229X.
PUB. COUNTRY: New Zealand
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 16 Oct 2001
Last Updated on STN: 4 Apr 2002
Entered Medline: 3 Apr 2002

AB It has been clearly established that lipid-lowering treatments [such as 3-hydroxyl-3-methylglutamyl coenzyme A reductase inhibitors ('statins') or fibrates] can reduce cardiovascular events, and with one of the statins even total mortality, in high-risk populations. Intervention studies have not included the very old, but it is generally assumed that this patient group would benefit from these treatments to an extent similar to younger patients. Worries about the associations seen in observational studies between low cholesterol levels and cancer, cerebral haemorrhage or mood and behaviour change have been largely overcome by findings from the latest large drug intervention trials, which do not show any increase in these conditions with statin or fibrate treatments. The common adverse effects associated with these drugs are relatively mild and often transient in nature. Potentially more serious adverse effects, which are more clearly related to drug treatment and are probably dose-dependent, include elevations in hepatic transaminase levels and myopathy; however, these effects are uncommon and generally resolve rapidly when treatment is stopped. The risk of myopathy with fibrate treatment is increased in patients with renal impairment, and the risk of myopathy with statin treatment increases with co-administration of drugs that inhibit statin metabolism or transport. Other adverse effects are related to specific drugs, for example, clofibrate is associated with an increased risk of gallstones. Studies in elderly patients have not shown an increased risk of adverse effects with lipid-lowering drugs compared with younger patients, but in clinical practice there may be some increased risk, particularly with regards to drug interactions. Therefore, lipid-lowering drugs should be administered with extra caution to elderly patients.

L7 ANSWER 5 OF 23 MEDLINE on STN
ACCESSION NUMBER: 2001333878 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 11401753
TITLE: Is peroxisome proliferation an obligatory precursor step in the carcinogenicity of di(2-ethylhexyl)phthalate (DEHP)?.
AUTHOR: Melnick R L
CORPORATE SOURCE: National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina 27709, USA.. melnickr@niehs.nih.gov
SOURCE: Environmental health perspectives, (2001 May) Vol. 109, No. 5, pp. 437-42. Ref: 55
Journal code: 0330411. ISSN: 0091-6765.
PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 27 Aug 2001
Last Updated on STN: 3 Apr 2002
Entered Medline: 23 Aug 2001

AB Di(2-ethylhexyl)phthalate (DEHP), a peroxisome proliferator, has been listed by the International Agency for Research on Cancer (IARC) and by the National Toxicology Program as a possible or reasonably anticipated human carcinogen because it induces dose-related increases in liver tumors in both sexes of rats and mice. Recently, the suggestion has been advanced that DEHP should be considered unlikely to be a human carcinogen because it is claimed that the carcinogenic effects of this agent in rodents are due to peroxisome proliferation and that humans are nonresponsive to this process. An IARC working group recently downgraded DEHP to "not classifiable as to its carcinogenicity to humans" because they concluded that DEHP produces liver tumors in rats and mice by a mechanism involving peroxisome proliferation, which they considered to be not relevant to humans. The literature review presented in this commentary reveals that, although our knowledge of the mechanism of peroxisome proliferation has advanced greatly over the past 10 years, our understanding of the mechanism(s) of carcinogenicty of peroxisome proliferators remains incomplete. Most important is that published studies have not established peroxisome proliferation per se as an obligatory pathway in the carcinogenicity of DEHP. No epidemiologic studies have been reported on the potential carcinogenicity of DEHP, and cancer epidemiologic studies of hypolipidemic fibrate drugs (peroxisome proliferators) are inconclusive. Most of the pleiotropic effects of peroxisome proliferators are mediated by the peroxisome proliferator activated receptor (PPAR), a ligand-activated transcription factor that is expressed at lower levels in humans than in rats and mice. In spite of this species difference in PPAR expression, hypolipidemic fibrates have been shown to induce hypolipidemia in humans and to modulate gene expression (e.g., genes regulating lipid homeostasis) in human hepatocytes by PPAR activation. Thus, humans are responsive to agents that induce peroxisome proliferation in rats and mice. Because peroxisome proliferators can affect multiple signaling pathways by transcriptional activation of PPAR-regulated genes, it is likely that alterations in specific regulated pathways (e.g., suppression of apoptosis, protooncogene expression) are involved in tumor induction by peroxisome proliferators. In addition, because DEHP also induces biological effects that occur independently of peroxisome proliferation (e.g., morphologic cell transformation and decreased levels of gap junction intercellular communication), it is possible that some of these responses also contribute to the carcinogenicity of this chemical. Last, species differences in tissue expression of PPARs indicate that it may not be appropriate to expect exact site correspondence for potential PPAR-mediated effects induced by peroxisome proliferators in animals and humans. Because peroxisome proliferation has not been established as an obligatory step in the carcinogenicity of DEHP, the contention that DEHP poses no carcinogenic risk to humans because of species differences in peroxisome proliferation should be viewed as an unvalidated hypothesis.

L7 ANSWER 6 OF 23 MEDLINE on STN
ACCESSION NUMBER: 2000436812 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 10947870
TITLE: Peroxisome proliferator-activated receptors in tumorigenesis: targets of tumour promotion and treatment.
AUTHOR: Roberts-Thomson S J
CORPORATE SOURCE: School of Pharmacy, The University of Queensland, St Lucia,

Australia.. s.roberts-thomson@pharmacy.uq.edu.au
SOURCE: Immunology and cell biology, (2000 Aug) Vol. 78, No. 4, pp. 436-41. Ref: 87
Journal code: 8706300. ISSN: 0818-9641.
PUB. COUNTRY: Australia
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 28 Sep 2000
Last Updated on STN: 28 Sep 2000
Entered Medline: 15 Sep 2000

AB The peroxisome proliferator-activated receptors (PPAR) are ligand-activated transcription factors. There are three genes that code for the PPAR isoforms: PPARalpha, PPARbeta and PPARgamma. In the present review, studies characterizing the various PPAR isoforms are discussed. Peroxisome proliferator-activated receptor alpha has been implicated in the lipid-lowering effects of the fibrate drugs. Peroxisome proliferator-activated receptor gamma has a clear role in adipocyte differentiation and is therapeutically targeted by the thiazolidinedione drugs for the treatment of type II diabetes. The physiological role of PPARbeta is less well understood but, as described in the present review, recent studies have implicated it with a role in colon cancer. In the present review, particular attention is focused on the role of PPAR in the regulation of expression of proteins associated with cell cycle control and tumorigenesis.

L7 ANSWER 7 OF 23 MEDLINE on STN
ACCESSION NUMBER: 1999340883 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 10412372
TITLE: An update on the mechanisms of action of the peroxisome proliferator-activated receptors (PPARs) and their roles in inflammation and cancer.
AUTHOR: Gelman L; Fruchart J C; Auwerx J
CORPORATE SOURCE: INSERM U 325, Departement d'Atherosclerose, Institut Pasteur, Lille, France.
SOURCE: Cellular and molecular life sciences : CMLS, (1999 Jun) Vol. 55, No. 6-7, pp. 932-43. Ref: 141
Journal code: 9705402. ISSN: 1420-682X.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 20 Aug 1999
Last Updated on STN: 20 Aug 1999
Entered Medline: 12 Aug 1999

AB Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors and have been initially described as molecular targets for compounds which induce peroxisome proliferation. The interest of researchers for PPARs increased dramatically when these receptors were shown to be directly activated by a number of medically relevant compounds. These compounds include: the fibrate class of hypolidemic drugs, the thiazolidinediones, which are insulin sensitizers used as orally active antidiabetic agents, certain non-steroidal anti-inflammatory drugs (NSAIDs), and naturally occurring fatty acid-derived molecules. Rapidly, it was demonstrated that PPARs are key regulators of lipid homeostasis and provide a molecular link between nutrition and gene regulation. Recently, detailed studies of PPAR expression profiles in

different tissues pointed to the roles these receptors play in inflammation control and cell proliferation. In this review we will focus on the new insights gained into these two areas and we will also discuss our current knowledge of the regulation of PPAR transcriptional activity by cofactors.

L7 ANSWER 8 OF 23 MEDLINE on STN
ACCESSION NUMBER: 1999124642 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 9924174
TITLE: Peroxisome proliferator-activated receptor alpha: role in rodent liver cancer and species differences.
AUTHOR: Holden P R; Tugwood J D
CORPORATE SOURCE: Zeneca Central Toxicology Laboratory, Alderley Park, Macclesfield, SK10 4TJ, UK.
SOURCE: Journal of molecular endocrinology, (1999 Feb) Vol. 22, No. 1, pp. 1-8. Ref: 70
Journal code: 8902617. ISSN: 0952-5041.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199903
ENTRY DATE: Entered STN: 13 Apr 1999
Last Updated on STN: 13 Apr 1999
Entered Medline: 30 Mar 1999

AB Peroxisome proliferators (PPs) are chemicals of industrial and pharmaceutical importance that elicit liver carcinogenesis by a non-genotoxic mechanism. One of the intriguing properties of PPs is that the pleiotropic effects of these compounds (including increased DNA synthesis and peroxisome proliferation) are seen in rats and mice only, but not humans. It is important to determine the risks to humans of environmental and therapeutic exposure to these compounds by understanding the mechanisms of non-genotoxic hepatocarcinogenesis in rodents. To understand this apparent lack of human susceptibility, attention has focused on the peroxisome proliferator-activated receptor alpha (PPARalpha), which appears to mediate the effects of PPs in rodents. It is also known to mediate the hypolipidaemic effects that fibrate drugs exert on humans with elevated plasma cholesterol and triglyceride levels. Human PPARalphas share many functional characteristics with the rodent receptors, in that they can be transcriptionally activated by PPs and regulate specific gene expression. However, one key difference is that PPARalpha is less abundant in human than in rodent liver, which has led to the suggestion that species differences result from quantitative differences in gene expression. In this review we describe the effects of PPs and what is known of the molecular mechanisms of action and species differences with respect to rodents and man. Attention will be given to differences in the amounts of PPARalpha between species as well as the 'qualitative' aspects of PPARalpha-mediated gene regulation which might also explain the activation of some genes and not of others in human liver by PPs.

L7 ANSWER 9 OF 23 MEDLINE on STN
ACCESSION NUMBER: 95191461 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 7885288
TITLE: Serum retinol levels throughout 2 years of cholesterol-lowering therapy.
AUTHOR: Muggeo M; Zenti M G; Travia D; Sartori A; Trimeloni S; Grigolini L; Graziani M S; Cigolini M
CORPORATE SOURCE: Cattedra di Malattie del Ricambio, Istituto di Chimica Clinica, Universita di Verona, Italy.

SOURCE: Metabolism: clinical and experimental, (1995 Mar) Vol. 44, No. 3, pp. 398-403.
Journal code: 0375267. ISSN: 0026-0495.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199504
ENTRY DATE: Entered STN: 25 Apr 1995
Last Updated on STN: 25 Apr 1995
Entered Medline: 12 Apr 1995

AB Some studies have reported an inverse correlation between serum cholesterol level and risk of cancer. This correlation might be due to a decrease in serum retinol, a lipid-soluble vitamin that controls cell proliferation and differentiation. We evaluated the influence of cholesterol-lowering therapy on serum retinol in 102 subjects (mean +/- SE: aged 47.1 +/- 4.1 years; body mass index, 23.8 +/- 0.6 kg/m2) with primary hypercholesterolemia treated for 2 years with different therapeutic protocols. Twenty-two subjects had been treated with diet alone, 35 with diet and fibrates, 37 with diet and hepatic hydroxymethyl glutaryl coenzyme A (HMG CoA) reductase inhibitors (statins), and eight with diet and cholestyramine. Postabsorptive serum retinol, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglyceride levels were determined at baseline and every 3 months. Baseline TC and LDL-C were significantly lower in the diet-treated group than in other groups. No intergroup differences were found in pretreatment levels of triglycerides and serum retinol. After 2 years of treatment, TC and LDL-C serum levels were not significantly decreased in the diet-alone group, whereas they were decreased by 20% and 24%, respectively, in the gemfibrozil group, 28% and 34% in the statins group; and 21% and 27% in the cholestyramine group. In the entire population (N = 102), serum retinol was 3.46 +/- 0.08 mumol/L before therapy and 3.76 +/- 0.07 after 2 years of therapy (P < .001). Serum retinol increased in diet- and statin-treated groups, but not in fibrate- and resin-treated groups.(ABSTRACT TRUNCATED AT 250 WORDS)

L7 ANSWER 10 OF 23 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:424121 CAPLUS Full-text
DOCUMENT NUMBER: 143:364123
TITLE: Advances in understanding the regulation of apoptosis and mitosis by peroxisome-proliferator activated receptors in pre-clinical models: Relevance for human health and disease
AUTHOR(S): Boitier, Eric; Gautier, Jean-Charles; Roberts, Ruth
CORPORATE SOURCE: Aventis Pharma Drug Safety Evaluation, Centre de Recherche de Paris, Paris, Fr.
SOURCE: Comparative Hepatology (2003), 2, No pp. given
CODEN: CHOEAJ; ISSN: 1476-5926
URL: http://www.comparative-hepatology.com/content/pdf/1476-5926-2-3.pdf
PUBLISHER: BioMed Central Ltd.
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English

AB A review. Peroxisome proliferator activated receptors (PPARs) are a family of related receptors implicated in a diverse array of biol. processes. There are 3 main isotypes of PPARs known as PPARα, PPARβ and PPARγ and each is organized into domains associated with a function such as ligand binding, activation and DNA binding. PPARs are activated by ligands, which can be both endogenous such as fatty acids or their derivs., or synthetic, such as peroxisome proliferators, hypolipidemic drugs, anti-inflammatory or insulin-sensitizing

drugs. Once activated, PPARs bind to DNA and regulate gene transcription. The different isotypes differ in their expression patterns, lending clues on their function. PPARα is expressed mainly in liver whereas PPARγ is expressed in fat and in some macrophages. Activation of PPARα in rodent liver is associated with peroxisome proliferation and with suppression of apoptosis and induction of cell proliferation. The mechanism by which activation of PPARα regulates apoptosis and proliferation is unclear but is likely to involve target gene transcription. Similarly, PPARγ is involved in the induction of cell growth arrest occurring during the differentiation process of fibroblasts to adipocytes. However, it has been implicated in the regulation of cell cycle and cell proliferation in colon cancer models. Less in known concerning PPARβ but it was identified as a downstream target gene for APC/β-catenin/T cell factor-4 tumor suppressor pathway, which is involved in the regulation of growth promoting genes such as c-myc and cyclin D1. Marked species and tissue differences in the expression of PPARs complicate the extrapolation of pre-clin. data to humans. For example, PPARα ligands such as the hypolipidemic fibrates have been used extensively in the clinic over the past 20 years to treat cardiovascular disease and side effects of clin. fibrate use are rare, despite the observation that these compds. are rodent carcinogens. Similarly, adverse clin. responses have been seen with PPARγ ligands that were not predicted by pre-clin. models. Here, we consider the response to PPAR ligands seen in pre-clin. models of efficacy and safety in the context of human health and disease.

REFERENCE COUNT: 167 THERE ARE 167 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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